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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/502,426	AZPIROZ ET AL.
	Examiner	Art Unit
	Ashwin Mehta	1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-57 is/are pending in the application.

4a) Of the above claim(s) 52-57 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 & 12 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-16, 18-35, 38-45, and 49-51 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that Groups IV and VI share the same classification, and Groups II and III share the same classification. Applicants also argue that a search of the art for sequences relevant to Group I would necessarily reveal art relevant to the remaining Groups, especially in light of the dependence of Groups II, V and VI claims on claims from Group I. Applicants argue that because of the close interrelatedness it would not be a serious burden on the Examiner to search and examine the inventions of these Groups together. During the course of examination of Group I, it was determined that examination of Groups II and III would not impose an undue burden, and claims 17, 36, 37, and 46-48 have been rejoined with the claims of Group I. However, Applicant's argument was not found persuasive for Groups IV-VI. Groups IV and VI are classified into different subclasses. Further, a search of the nucleotide sequences of the claims of Group I would not necessarily reveal art relevant Groups IV-VI. A search for the polypeptides of Groups IV and VI would not necessarily teach the genes or cDNAs encoding them. The invention of Group V is drawn to a polynucleotide fusion, whereas the nucleotide sequence of the invention of Groups I-III is not. As the other groups are drawn to different sequences, the claims of each group do not share a close interrelatedness, and therefore would impose a serious burden to the Examiner to search and examine them together.

The requirement for restriction of the claims of Groups IV-VI is still deemed proper and is therefore made FINAL. Claims 52-57 are withdrawn from consideration for being drawn to non-elected inventions and require cancellation.

Information Disclosure Statement

2. The reference designated "AF-1" in the supplemental information disclosure statement (IDS) submitted 09 October 2001 is identical to the reference designated "AE-1", and has therefore been lined through. It is also noted that a copy of a reference was submitted with that same IDS, but its bibliographic information was not included in the statement. The reference has been made of record on the accompanying Notice of References cited.

Specification

3. The specification is objected to for the following reasons:

Page 18, line 5 and page 51, line 27, contain embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification fails to comply with 37 CFR 1.821-1.825 because Figure 3 contains sequences that are required to be identified by sequence identifiers.

The sentence spanning lines 24-25 of page 30 indicates that the coding region of the dwf4 gene is designated in Figure 10 by a light gray bar. While a colorless bar depicts the exons of the dwf4 gene nucleotide sequence shown in Figure 10, a light gray bar indicating the coding region is not present. Clarification is required.

The sentence spanning lines 28-30 of page 55 indicates that Figure 6 contains phylogenetic analysis. Figure 6 does not show a phylogenetic analysis, but one is shown in Figure 3. Clarification is required. New matter must be avoided.

Claim Objections

4. Claims 3, 7, and 22 are objected to.

Claims 3 and 7 are objected to under 37 CFR 1.75 (b) as being duplicate claims. While the claims from which claims 3 and 7 depend are not co-extensive in scope, claims 3 and 7 both limit the polynucleotides of their parent claims to comprise SEQ ID NO: 1, complements and reverse complements thereof. Applicant is required to cancel one of the claims, or amend the claim(s).

Regarding claim 22: "intro" in line 4 is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 5-7, 9-45, and 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "at least about" in line 3 of claims 1 and 5 render the claims indefinite. The recitation makes the metes and bounds of the claims unclear.

In 2, 3, and 5-7: the recitation "complements and reverse complements thereof" renders the claims indefinite. There can only be one complement and reverse complement of a given nucleotide sequence.

In claim 5: in part (ii), it is not clear whether it is the sequence, or the 15 contiguous nucleotides that has at least 50% identity to SEQ ID NO: 1.

In claims 11, 12, and 24: the recitation "control elements" in line 2 of claims 11 and 12 and "control element" in line 2 of claim 24 renders the claims indefinite. The definition for control element on page 20, line 31 recites the recitation "Typical "control elements", include, but are not limited to". It is not clear what other elements can be considered a "control element" except for those listed on pages 20 and 21.

In claims 11 and 12: the recitation "control elements operably linked to said polynucleotide" in line 2 of the claims renders them indefinite. The polynucleotides of the parent claims encompass genomic sequences, which inherently comprise promoters, transcription terminators and introns. It is not clear whether claims 11 and 12 are referring to the control elements found within the polynucleotides of their parent claims, or to different control elements.

In claim 15: the recitation "modulating a DWF4 polypeptide" renders the claim indefinite. It is not clear what "modulating" exactly encompasses. For example, is the recitation referring to increasing the expression of a DWF4 polypeptide, decreasing the expression, altering its structure, altering its activity, etc.

In claims 20-22: the recitation "includes" renders the claims indefinite. It is not clear whether the term refers to open or closed language.

In claim 24: it is not clear if the "nucleic acid molecule comprising a coding sequence" of part (b) is the dwf4 polynucleotide of parent claim 5. Part (a) of claim 24 indicates that the claimed vector comprises a dwf4 control element of claim 20. However, claim 20 is directed to the isolated polynucleotide of claim 5. It is therefore not clear whether the molecule of part (b) of claim 24 is referring to the dwf4 coding sequence, to another coding sequence, or if the dwf4 coding sequences are comprised within the claimed vector. There is also improper antecedent basis for "a dwf4 control element of claim 20", as claim 20 is directed to the isolated polynucleotide of claim 5.

In claim 28: the claim recites the limitation "the wild-type plant" in line 2. There is insufficient antecedent basis for this limitation in the claim, or the claim from which it depends.

In claim 34: the claim is indefinite because it employs incorrect Markush terminology. Examples of proper Markush terminology, for a hypothetical claim in which an item from a group consisting of A, B, C, and D, is to be chosen, are 1) the chosen item is A, B, C, or D; or 2) the chosen item is selected from the group consisting of A, B, C, and D. See MPEP § 2173.05(h).

In claim 29: the claim recites the limitation "the phenotype" in line 1. There is insufficient antecedent basis for this limitation in the claim, or the claims from which it depends. The recitation "regulation of brassiniosteroids, regulation of gibberellic acids, regulation of cytokinins, regulation of auxins" in lines 5-6 of claim 29 also renders the claim indefinite. Claim 29 is drawn to a method of altering a phenotype. However, the "regulation of" a substance is not a phenotype.

In claim 37: the claim does not clearly indicate the "first and second polynucleotides" in line 1 are both isolated dwf4 polynucleotides of claim 5. Note that if they are not, then claim 37 broadens rather than limits the scope of claim 28.

In claim 49: the recitation "method of according to claim 25" in line 1 renders the claim indefinite. The meaning of the recitation is unknown, and therefore what the claim is directed to is unknown. Further, claim 25 is directed to a host cell, not a method. Claim 49 also recites the limitation "the DWF4 polypeptide" in line 1. There is insufficient antecedent basis for this limitation in the claim, or the claims from which it depends.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 4-6, and 8-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn towards any isolated dwf4 polynucleotide comprising an open reading frame encoding a polypeptide comprising (i) a sequence having greater than 43% identity to the amino acid sequence of SEQ ID NO: 2; (ii) a sequence comprising at least about 10 amino acids having greater than 43% identity to any 10 contiguous amino acid sequences of SEQ ID NO: 2, or a complement or reverse complement of said polynucleotide; or wherein the polynucleotide has at least 70% identity to the DWF4 polypeptide-coding region of SEQ ID NO:

1, complements and reverse complements thereof; or wherein the polynucleotide comprises at least any 30 consecutive nucleotides of SEQ ID NO: 1; or an isolated dwf4 polynucleotide comprising a sequence having at least 50% identity to SEQ ID NO: 1, or a sequence comprising at least about 15 contiguous nucleotides that have at least 50% identity to SEQ ID NO: 1, complements or reverse complements thereof; or wherein said polynucleotide is genomic DNA, or includes introns; or a recombinant vector comprising said polynucleotide operably linked to control elements whereby a coding sequence within said polynucleotide can be transcribed in a host cell; a host cell comprising said vector; a method of modulating a DWF4 polypeptide comprising providing culturing said host cell whereby the dwf4 polynucleotide is transcribed; a transgenic plant comprising said vector; said polynucleotide including any dwf4 control element comprising a polynucleotide having sequences having at least 50% identity to nucleotides 1-3202 of SEQ ID NO: 2 or any fragment thereof which includes a dwf4 control element, and complements and reverse complements thereof; or wherein said dwf4 control element is a sequence having at least 50% identity to nucleotides 6111-6468 corresponding to the 3' UTR of SEQ ID NO: 1, or any fragment thereof which includes any dwf4 3' UTR, and complements and reverse complements thereof; or wherein said dwf4 control element comprises a polynucleotide sequence having at least 50% identity to the sequences corresponding to the introns of SEQ ID NO: 1, or any fragment thereof that includes a dwf4 intron, and complements and reverse complements thereof; or a recombinant vector comprising said polynucleotide including said dwf4 control element, and a nucleic acid molecule comprising a coding sequence; any host cell transformed with said vector; a method of producing any recombinant polypeptide comprising culturing said host cell; a method of producing a transgenic plant having an altered phenotype; a

method for altering any biochemical activity of any cell; a method for regulating the cell cycle of a plant cell.

The specification describes the isolation and sequencing of a genomic clone (SEQ ID NO: 1) encoding the Arabidopsis DWF4 polypeptide (SEQ ID NO: 2; page 48, line 16 to page 52, line 25). The specification also indicates that the DWF4 polypeptide of SEQ ID NO: 2 is a cytochrome P450 monooxygenase (page 52, lines 27-29), and that it is most similar protein to another Arabidopsis cytochrome p450, CPD, with which it shares 43% identity and 66% similarity (page 54, lines 18-27). The specification at page 30, lines 24-28 indicates that the coding region begins at nucleotide position 1133. Figure 2 describes the locations of exon, introns, 5' and 3' untranslated regions of the genomic clone, as well as the locations of four domains in DWF4 that are found in cytochrome P450 proteins. The specification at page 71, line 30 to page 72, line 10 indicates that a 1.1 kb region of the genomic clone upstream of the translation initiation start was used a the promoter fragment in DWF4-promoter::GUS constructs. The specification at page 69, line 30 to page 70, line 7 indicates that the Arabidopsis DWF4 polypeptide is a 22α-hydroxylase that catalyzes the two 22α-hydroxylation steps of the brassinolide (BL) biosynthetic pathway (Figure 1).

However, the specification does not teach the nucleotide sequence of any other dwf4 polynucleotide, or their control elements. The specification at page 54, line 27 to page 54, line 3 indicates that SEQ ID NO: 2 possesses four domains that are typical of cytochrome P450s. As these four domains are present in other cytochrome P450s, the presence of these domains in proteins having more than 43% identity to SEQ ID NO: 2 or that comprise at least about any 10 contiguous amino acid having greater than 43% SEQ ID NO: 2 to any 10 contiguous amino acids

of SEQ ID NO: 2 (or polypeptides encoded by polynucleotides having at least 50% identity to SEQ ID NO: 1 or comprising at least about 15 contiguous nucleotides that have at least 50% identity to any 15 contiguous nucleotides of SEQ ID NO: 1), is not an indication that it has the same enzymatic activity as SEQ ID NO: 2. The correlation of the other amino acid sequences of SEQ ID NO: 2 to its functional enzymatic activity is also not described. Further, given that the aforementioned domain themselves are more than 10 amino acids in length, it is not clear how any polypeptide having only at least about any 10 contiguous amino acids having just over 43% identity with any 10 contiguous amino acids of SEQ ID NO: 2, or any polypeptide encoded by a polynucleotide having only at least about any 15 contiguous nucleotides having at least 50% identity to SEQ ID NO: 1, can have the functional enzymatic activity of SEQ ID NO: 2. As SEQ ID NO: 1 includes sequences that are not a part of the dwf4 gene, polynucleotide comprising at least 30 nucleotides of SEQ ID NO: 1 encompass nucleotide sequences that are not related to SEQ ID NO: 1, and are not described by the specification. Also see Fiers vs. Sugarno, 25 USPQ 2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself".

Furtherstill, the specification indicates that bases 990-1132 of SEQ ID NO: 1 and a 1.1 kb fragment downstream of the translation start site comprises dwf4 promoter activity. The specification does not describe any other fragment of bases 1-3200 of SEQ ID NO: 2 that includes a dwf4 control element. Furthermore, page 75, lines 12-15 indicates that the 1.1kb fragment, rather than a 240 bp fragment comprising a TATA-like promoter region, is required for promoter activity. It is therefore not clear that the fragment spanning bases 990-1132 of SEQ

ID NO: 1 represent a promoter fragment, as it is smaller than the 240 bp fragment. The failure of the 240 bp fragment to properly control dwf4 transcription also indicates that sequences that resemble promoter control regions are not an indication that they actually are control elements. The specification also does not describe fragments of nucleotides 6111-6468 of SEQ ID NO: 1 which are also control elements. Given the breadth of the claims and lack of guidance of the specification as discussed above, the specification fails to provide an adequate written description of the multitude of polynucleotide sequences encompassed by the claims.

7. Claims 1-45 and 49-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleotide sequences encoding SEQ ID NO: 2, the promoter activity of bases 1-3202 and a 1.1 kb region downstream from the translational start site in SEQ ID NO: 1, a method to produce transgenic plants overexpressing SEQ ID NO: 2 displaying some of the phenotypes and changes in biochemical activity listed in the claims, and host plant and bacterial cells, does not reasonably provide enablement for nucleotide sequences encoding polypeptides that differ from SEQ ID NO: 2 while retaining its functional activity, sequences comprising any type of control element that differ from bases 1-3202 of SEQ ID NO: 1, a method to inhibit expression of dwf4 polynucleotides, methods to alter all of the phenotypes in plants or biochemical activities in cells listed in the claims, methods comprising inhibiting dwf4 polynucleotide expression, and all host cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn towards any isolated dwf4 polynucleotide comprising an open reading frame encoding a polypeptide comprising (i) a sequence having greater than 43% identity to the amino acid sequence of SEQ ID NO: 2; (ii) a sequence comprising at least about 10 amino acids having greater than 43% identity to any 10 contiguous amino acid sequences of SEQ ID NO: 2, or a complement or reverse complement of said polynucleotide; or wherein the polynucleotide has at least 70% identity to the DWF4 polypeptide-coding region of SEQ ID NO: 1, complements and reverse complements thereof; or wherein the polynucleotide comprises at least any 30 consecutive nucleotides of SEQ ID NO: 1; or an isolated dwf4 polynucleotide comprising a sequence having at least 50% identity to SEQ ID NO: 1, or a sequence comprising at least about 15 contiguous nucleotides that have at least 50% identity to SEQ ID NO: 1, complements or reverse complements thereof; or wherein said polynucleotide is genomic DNA, or includes introns; or a recombinant vector comprising said polynucleotide operably linked to control elements whereby a coding sequence within said polynucleotide can be transcribed in a host cell; a host cell comprising said vector; a method of modulating a DWF4 polypeptide comprising providing culturing said host cell whereby the dwf4 polynucleotide is transcribed; a transgenic plant comprising said vector; said polynucleotide including any dwf4 control element comprising a polynucleotide having sequences having at least 50% identity to nucleotides 1-3202 of SEQ ID NO: 2 or any fragment thereof which includes a dwf4 control element, and complements and reverse complements thereof; or wherein said dwf4 control element is a sequence having at least 50% identity to nucleotides 6111-6468 corresponding to the 3' UTR of SEQ ID NO: 1, or any fragment thereof which includes any dwf4 3' UTR, and complements and reverse complements thereof; or wherein said dwf4 control element comprises a polynucleotide

sequence having at least 50% identity to the sequences corresponding to the introns of SEQ ID NO: 1, or any fragment thereof that includes a dwf4 intron, and complements and reverse complements thereof; or a recombinant vector comprising said polynucleotide including said dwf4 control element, and a nucleic acid molecule comprising a coding sequence; any host cell transformed with said vector; a method of producing any recombinant polypeptide comprising culturing said host cell; a method of producing a transgenic plant having an altered phenotype; a method for altering any biochemical activity of any cell.

As discussed above, the specification teaches the isolation and sequence of a genomic clone (SEQ ID NO: 1) encoding the Arabidopsis DWF4 polypeptide (SEQ ID NO: 2), and that SEQ ID NO: 2 is a cytochrome P450 monooxygenase that is a 22α-hydroxylase that catalyzes the two 22α-hydroxylation steps of the brassinolide (BL) biosynthetic pathway. Also as discussed above, the specification teaches the start of the coding region in SEQ ID NO: 1, the locations of the introns and exons of SEQ ID NO: 1, and that a 1.1 kb region downstream of the translation start site comprises the promoter activity required for proper transcription of dwf4. The specification also teaches that mutant dwf4 mutant Arabidopsis plants have a dwarf phenotype, with short, rounded leaves (page 56, lines 16-18), and showed a delay in the start of flowering (page 57, lines 21-29, Table 1). The short stature of dwf4 mutant plants was due to a defect in cell elongation, as opposed to cell division (page 58, lines 20-30), and grew slower in the dark (page 62, lines 2-4). The dwf4 mutant plants were capable of perceiving gibberellic acid (GA) but failed to respond to exogenously applied GA. The dwf4 mutant plant also respond to inhibitory effects of auxin, but was incapable of auxin-stimulated elongation (page 62, lines 3-30). Exogenous application of BL restored wilt-type growth to the mutant plants (page 62, line

13-24). To determine the step of the BL biosynthetic pathway affected in the dwf4 mutant, the mutant plant was grown in medium supplemented with the different known pathway intermediates. 22-hydroxylated steroids rescued the mutant. The plants have no other defect other than in 22α-hydroxylation (page 67, line 23 to page 69, line 22). The specification also teaches the construction of recombinant vectors comprising the DWF4 coding region operably linked to the CaMV 35S promoter, and that transgenic Arabidopsis plants overexpressing DWF4 were produced (page 71, line 30 to page 77, line 23). Compared to non-transformed plants, DWF4 overexpression in transgenic plants resulted in increased plant height, larger leaves, increased seed production, and an increase in the number of branches.

The specification does not teach any other nucleotide sequence other than SEQ ID NO: 1 that encodes an enzyme that catalyzes the 22α-hydroxylation steps of the BL biosynthetic pathway. The specification teaches that the protein that is most similar to DWF4 is another cytochrome P450, CPD, with which it shares 43% identity and 66% similarity (page 54, lines 18-27). CPD acts on different substrates than DWF4 in the BL pathway (page 14, lines 26-30, Figure 1). However, it is highly inaccurate to simply assume that all amino acid sequences that have greater than 43% amino acid identity with SEQ ID NO: 2 will also share its functional activity. As discussed above, the specification teaches that DWF4 comprises four domains that are present in cytochrome P450 proteins. All of these proteins do not have the same functional activity. The specification does not teach the significance of the other amino acid sequences of DWF4 protein, and provide no guidance in how the sequence of SEQ ID NO: 1 or SEQ ID NO: 2 may be changed without altering its enzymatic function (other than differences due to genetic code degeneracy). Further, given that the aforementioned domains are greater than 10 amino

acids in length, it is unclear how a polypeptide having a sequence comprising at least about 10 contiguous amino acids having greater than only 43% identity to any 10 contiguous amino acids of SEQ ID NO: 2 can also retain its function. Likewise, it is unclear how a polynucleotide comprising at least about only 15 contiguous nucleotides having at least 50% identity to SEQ ID NO: 1 can encode a polypeptide that has the same functional activity as SEQ ID NO: 2. As SEQ ID NO: 1 represents a genomic clone comprising sequences that are not a part of the dwf4 gene, nucleotide sequences that comprise only at least any 30 consecutive nucleotides of SEQ ID NO: 1 include those that are not related to SEQ ID NO: 1, yet are encompassed by the claims. In the absence of further guidance, it would require one skilled undue experimentation to determine all of the changes that can be sustained by SEQ ID NO: 2 without altering its 22α-hydroxylase activity. Also see In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 UPSQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence). Further, the specification does not teach the use of any of the reverse complements of the claimed nucleotide sequences. Such sequences could encode other products, none of which are even mentioned in the specification.

As discussed above, the specification teaches that a 1.1kb fragment comprising sequences downstream from the translation start site (nucleotide 3202, Figure 10) comprises the sequences necessary for proper transcriptional control of the dwf4 gene. However, the specification does not teach that sequences that differ from bases 1-3202 of SEQ ID NO: 1 have any control

elements. However, even minor alterations of the nucleotide sequence of a promoter can negatively affect its regulatory activity. For example, Kim et al show that for the nopaline synthase promoter, changes affecting just a few nucleotides can abolish activity (page 106, paragraph bridging the columns; paragraph bridging pages 107 and 108; page 110, first column). Further, as discussed above the specification admits that a 208 bp region carrying a TATA-like region did not properly control dwf4 transcription. In the absence of further guidance, it would require undue experimentation to determine the changes that can be made to nucleotides 1-3202 without affecting its promoter activity. The specification does not teach any other type of control element in this region. Given that even minor sequence changes can abolish promoter activity, it is unpredictable which portions of SEQ ID NO: 10 would retain promoter activity. The specification also does not teach any control elements of reverse complements of any portion of SEQ ID NO: 1. The specification also makes no mention of control elements present in sequences that have at least 50% identity to nucleotides 6111-6468 of SEQ ID NO: 1, or fragments thereof, nor that sequences that have at least 50% identity to any intron of SEQ ID NO: 1, or any fragment thereof, will not interfere with the proper processing of the dwf4 transcript. See also Genentech, Inc. V. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

While the specification teaches that transgenic plants overexpressing the DWF4 of SEQ ID NO: 2 displays several altered phenotypes, as discussed above, it does not alter any other phenotype, or any other biochemical activity, as broadly encompassed by the claims. As discussed, transgenic plants overexpressing DWF4 showed increased plant height, increased

branches, increased seeds, larger leaves. Transgenic plants transformed with the coding region for SEQ ID NO: 2 display increased heme-thiolate activity, monooxygenase activity, and 22α-hydroxylase activity, only insofar as it is associated with DWF4. The transgenic plants do not regulate all brassinosteroids. Rather, as discussed above, the specification teaches that DWF4 is only involved in the BL pathway. Also as discussed above, there is no alteration in the regulation of gibberellic acid and auxins. As indicated above, the data collected from the analysis of the dwf4 mutant plant indicate that DWF4 may be required to respond to these compounds. A lack of response is not an indication that the regulation of the compounds themselves has changed. There is no teaching in the specification or in the prior art indicating that DWF4 regulates GAs, auxins, or cytokinins. There is no teaching in the specification or prior art that transgenic plants transformed with nucleotide sequences encoding SEQ ID NO: 2 have altered growth at low temperatures or altered resistance to any pathogens. The specification does not even indicate that the transgenic plants were tested for growth at low temperature or resistance to any plant pathogens at all. Further, the only sterol affected by DWF4 is BL. Choe et al. (Plant J., 2001, Vol. 26, pages 573-582) also teach transgenic Arabidopsis plants overexpressing DWF4. The plants showed increased growth, branching, and production of seeds, but were not altered in flowering time (page 576-577). Given that both the specification does not teach other alterations of the claimed transgenic plants overexpressing DWF4, it would require further guidance for one skilled in the art to use the claimed methods to alter all of the phenotypes and biochemical activities of plants and cells encompassed by the claims. See Genentech, Inc. V. Novo Nordisk, A/S, *supra*.

Further, while the specification teaches the phenotypes associated with dwf4 mutant plants, it is not predictable that transgenic plants can be produced by the claimed methods wherein dwf4 expression is inhibited, and wherein the transgenic plants also display the same phenotypes and changes in biochemical activity associated with dwf4 mutant plants. That is, given that numerous cytochrome P450 genes encode proteins that share conserved domains, the claimed nucleotide sequences, when used in the claimed methods to inhibit dwf4 expression, may also affect the expression of other cytochrome P450 genes. For example, Branch (Trends in Biochem. Sci., 1998, Vol. 23, pages 45-50) discusses how antisense sequences can affect unintended targets (pages 45-47). If other genes are affected, it is unpredictable what the effect on the transgenic plant would be, or if it would even be viable. As other cytochrome P450s are also involved in BL synthesis, as exemplified by CPD, the phenotype of the transgenic plant may be due to inhibition of other genes. One may not be able to distinguish phenotypes caused by inhibition of dwf4 versus other genes, if the gene affects the same biochemical pathways. As gene silencing is also attributed to shared sequence homologies between nucleotide sequences (reviewed in, for example, Stam et al., Annals of Botany, 1997, Vol. 79, pages 3-12), this other aspect of the claimed methods may also not yield plants or cells in which only dwf4 gene expression is inhibited. In the absence of further guidance, it would require undue experimentation by one skilled in the art to use the claimed methods to produce transgenic plants in which only dwf4 gene expression is inhibited and which display the same changes in phenotype and biochemical activity as dwf4 mutant plants, and distinguish the plants from those in which other genes have been affected.

Furtherstill, the specification only teaches use of the claimed polynucleotides with host cells that are plants or bacterial cells (which are routinely used in the art to store nucleotide sequences of interest). It is suggested that the claims be amended to encompass only plant and bacterial host cells. Given the breadth of the claims encompassing polynucleotides encoding polypeptides that differ from SEQ ID NO: 2, control elements that differ from those within SEQ ID NO: 1, methods to alter any phenotype of a transgenic plant or any biochemical activity of any cell, methods comprising inhibiting expression of dwf4 expression with the claimed polynucleotides, and any host cell, and reverse complements of the claimed polynucleotides, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

8. Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn towards a method for regulating the cell cycle of a plant cell.

As discussed above, the specification teaches that dwf4 mutant Arabidopsis plants are dwarf plants. The short stature of dwf4 mutant plants was due to a defect in cell elongation, as opposed to cell division (page 58, lines 20-30). Thus, the specification admits that DWF4 does not affect cell division. There is not teaching in the specification or the prior art that

overexpression of DWF4 results increased cell division, or that DWF4 affects any cell cycle protein. In the absence of further guidance, it would require undue experimentation for one skilled in the art to use the claimed method to regulate cell division. See Genentech, Inc. V. Novo Nordisk, A/S, *supra*. Further, as discussed above, the only dwf4 polynucleotide taught by the specification, and which can be used in the claimed method, is that encoding SEQ ID NO: 2. Given the breadth of the claims encompassing regulating the cell cycle of plant cells, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-14 and 20-25 are rejected under 35 U.S.C. 102(a) or 102(b), as being clearly anticipated by Choe et al. (Plant Cell, February [illegible], 1998, Vol. 10, pages 231-244).

The claims are broadly drawn towards any isolated dwf4 polynucleotide comprising an open reading frame encoding a polypeptide comprising (i) a sequence having greater than 43% identity to the amino acid sequence of SEQ ID NO: 2; (ii) a sequence comprising at least about

10 amino acids having greater than 43% identity to any 10 contiguous amino acid sequences of SEQ ID NO: 2, or a complement or reverse complement of said polynucleotide; or wherein the polynucleotide has at least 70% identity to the DWF4 polypeptide-coding region of SEQ ID NO: 1, complements and reverse complements thereof; or wherein the polynucleotide comprises at least any 30 consecutive nucleotides of SEQ ID NO: 1; or an isolated dwf4 polynucleotide comprising a sequence having at least 50% identity to SEQ ID NO: 1, or a sequence comprising at least about 15 contiguous nucleotides that have at least 50% identity to SEQ ID NO: 1, complements or reverse complements thereof; or wherein said polynucleotide is genomic DNA, or includes introns said polynucleotide including any dwf4 control element comprising a polynucleotide having sequences having at least 50% identity to nucleotides 1-3202 of SEQ ID NO: 2 or any fragment thereof which includes a dwf4 control element, and complements and reverse complements thereof; or wherein said dwf4 control element is a sequence having at least 50% identity to nucleotides 6111-6468 corresponding to the 3' UTR of SEQ ID NO: 1, or any fragment thereof which includes any dwf4 3' UTR, and complements and reverse complements thereof; or wherein said dwf4 control element comprises a polynucleotide sequence having at least 50% identity to the sequences corresponding to the introns of SEQ ID NO: 1, or any fragment thereof that includes a dwf4 intron, and complements and reverse complements thereof; or a recombinant vector comprising said polynucleotide including said dwf4 control element, and a nucleic acid molecule comprising a coding sequence; any host cell transformed with said vector.

Choe et al. teach the isolation and nucleotide sequence of instant SEQ ID NO: 1 and the locations of the exons and introns of the DWF4 gene comprised within it. It is inherent that SEQ

ID NO: 1 comprises all of its control elements. The sequence was comprised within a recombinant vector during its isolation. The vector comprised SEQ ID NO: 1, and therefore its operably linked control elements which are needed for its transcription and translation in a cell. The vector was introduced into *Escherichia coli* cells (pages 4-6, 14-15).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-16, 18-29, 31-35, 38-45, and 49-51 rejected under 35 U.S.C. 103(a) as being unpatentable over Choe et al. (Plant Cell, February 1998, Vol. 10, pages 231-244) in view of Applicant's admitted state of the prior art.

The claims are broadly drawn towards any isolated dwf4 polynucleotide comprising an open reading frame encoding a polypeptide comprising (i) a sequence having greater than 43% identity to the amino acid sequence of SEQ ID NO: 2; (ii) a sequence comprising at least about 10 amino acids having greater than 43% identity to any 10 contiguous amino acid sequences of SEQ ID NO: 2, or a complement or reverse complement of said polynucleotide; or wherein the polynucleotide has at least 70% identity to the DWF4 polypeptide-coding region of SEQ ID NO: 1, complements and reverse complements thereof; or wherein the polynucleotide comprises at least any 30 consecutive nucleotides of SEQ ID NO: 1; or an isolated dwf4 polynucleotide

comprising a sequence having at least 50% identity to SEQ ID NO: 1, or a sequence comprising at least about 15 contiguous nucleotides that have at least 50% identity to SEQ ID NO: 1, complements or reverse complements thereof; or wherein said polynucleotide is genomic DNA, or includes introns; or a recombinant vector comprising said polynucleotide operably linked to control elements whereby a coding sequence within said polynucleotide can be transcribed in a host cell; a host cell comprising said vector; a method of modulating a DWF4 polypeptide comprising providing culturing said host cell whereby the dwf4 polynucleotide is transcribed; a transgenic plant comprising said vector; said polynucleotide including any dwf4 control element comprising a polynucleotide having sequences having at least 50% identity to nucleotides 1-3202 of SEQ ID NO: 2 or any fragment thereof which includes a dwf4 control element, and complements and reverse complements thereof; or wherein said dwf4 control element is a sequence having at least 50% identity to nucleotides 6111-6468 corresponding to the 3' UTR of SEQ ID NO: 1, or any fragment thereof which includes any dwf4 3' UTR, and complements and reverse complements thereof; or wherein said dwf4 control element comprises a polynucleotide sequence having at least 50% identity to the sequences corresponding to the introns of SEQ ID NO: 1, or any fragment thereof that includes a dwf4 intron, and complements and reverse complements thereof; or a recombinant vector comprising said polynucleotide including said dwf4 control element, and a nucleic acid molecule comprising a coding sequence; any host cell transformed with said vector; a method of producing any recombinant polypeptide comprising culturing said host cell; a method of producing a transgenic plant having an altered phenotype; a method for altering any biochemical activity of any cell.

Choe et al. is discussed above. Choe et al. also teach that brassinosteroids are important in plant growth promotion, and that DWF4 is a 22a-hydrozylase that provides the 22a-hyroxylase activity in the BL biosynthetic pathway (pages 2, 8-11).

Choe et al. do not teach plant transformation vectors, plant inducible, constitutive, and tissue-specific promoters, plant transformation techniques and regeneration of plants from plant cells.

Applicant's admitted state of the prior art teaches plant transformation vectors, inducible, constitutive and tissue-specific promoters, and plant transformation techniques, and regeneration of plants from transformed plant cells (page 36, line 5 to page 39, line 14).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to produce transgenic plants overexpressing the DWF4-encoding polynucleotide of Choe et al. Any one of a number plant expression vectors, plant transformation and regeneration techniques could have been used, including those taught in Applicant's admitted state of the prior art. As DWF4 is involved in the biosynthesis of the brassinosteroid, brassinolide, and brassinosteroids are promote plant growth, as taught by Choe et al., the transgenic plant would be larger than corresponding non-transformed plants. As brassinosteroids promote growth, it is obvious that plant parts, including leaves, would be larger as well. Any one of a variety of promoters may be used, including any one of the promoters taught in Applicant's admitted state of the prior art, to achieve a desired result. As DWF4 is a 22α-hydroxylase, it would have been obvious that the transgenic plants would have higher 22α-hydroxylase activity. If a plant cells or protoplasts are transformed, it is obvious that the transformed cells would first be cultured *ex vivo*. The plant transformation techniques taught by

Applicant's admitted state of the prior art include transformation of plants and plant cells. One would have been motivated to produce such transgenic plants, given the teaching of Choe et al. that brassinosteroids promote plant growth, and the obvious advantages provided by the production of larger plants.

11. No claim is allowed.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 703-306-4540. The examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at 703-308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

A.M.
December 3, 2001

PHUONG T. BUI
PRIMARY EXAMINER